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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,047	12/07/2000	Edwin F. Ullman	BEH-7385	9672

34500 7590 03/28/2005

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EXAMINER	
VENCI, DAVID J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/732,047	ULLMAN ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 27, 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 37-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 37-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *May 7, 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' amendment filed December 27, 2004, which amended claims 1-4, added new claims 37-46, and cancelled claims 9 and 25-36. Currently, claims 1-6 and 37-46 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

The drawings are objected to because Figs. 9 and 10 are unreadable (e.g. bars are indistinguishable). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

Claims 1-6 and 37-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specific claim rejections under 35 USC 112, second paragraph, set forth infra, may be considered relevant to other claims not explicitly mentioned, as deemed reasonably appropriate.

In claims 1 and 44, the recitation of the term "substrate" is indefinite because Applicants' specification appears to use the term "substrate" interchangeably with "product" and "surface." For example, Applicants describe a "substrate" that is associated with, and releasable from, a "support" (see p. 4, lines 20-21, "oxidant cleavable linker may be used to attach substrate molecules... to a surface") (see p. 5, lines 11, "release of the substrate"). However, Applicants also describe a "product" that is associated with, and releasable from, a "support" and a "substrate" (see p. 4, lines 24-26, "The resulting detectable product is released from the surface or support and is physically separated from the substrate by centrifugation, decantation...") (see p. 5, lines 13-14, "the invention does not require separation of the product from the substrate").

In claim 1, the recitation of "or indirectly" is indefinite because it is not clear what type of spatial relationship is created by "indirectly" binding or which entities are included in the binding interaction. Furthermore, a person of ordinary skill in the art cannot ascertain the standard or degree of indirectness required by "indirectly."

In claim 3, it is not clear how the "step of detecting the released detectable substrate..." is incorporated into the method of claim 1. For example, it is not clear whether "avidin" or "anti-digoxigenin antibodies" of claim 3 are used in addition to, or in place of, the "third specific binding pair member" of claim 1. In addition, the purpose of using both "avidin" and "anti-digoxigenin antibodies" to detect a single substrate is not clear. In addition, the recitation of "signal producing system" is indefinite because it is not clear what entities consist of, or comprise, a "signal producing system" or whether/how such entities are bound to "avidin" and "anti-digoxigenin antibodies" or how such entities function in the step of detection.

Applicants' specification states that a signal producing system includes "all of the reagents required to produce a measurable signal." It is not clear whether/how "all of the reagents required to produce a measurable signal" are bound to "avidin" and "anti-digoxigenin antibodies." In addition, it is not clear why more than one "signal producing system" is needed, or why it is necessary to duplicate the "signal producing system" of claim 1.

In claim 46, it is not clear how the "step of detecting the released detectable substrate..." is incorporated into the method of claim 44. For example, it is not clear whether "avidin" or "anti-digoxigenin antibodies" of claim 46 are used in addition to, or in place of, the "first specific binding pair member" "or second specific binding pair member" of claim 44. In addition, the purpose of using both "avidin" and "anti-digoxigenin antibodies" to detect a single substrate is not clear. In addition, the recitation of "signal producing system" is indefinite because it is not clear what entities consist of, or comprise, a "signal producing system" or whether/how such entities are bound to "avidin" and "anti-digoxigenin antibodies" or how such entities function in the step of detection. Applicants' specification states that a signal producing system includes "all of the reagents required to produce a measurable signal." It is not clear whether/how "all of the reagents required to produce a measurable signal" are bound to "avidin" and "anti-digoxigenin antibodies." In addition, it is not clear why more than one "signal producing system" is needed, or why it is necessary to duplicate the "signal producing system" of claim 44.

Claim Rejections - 35 USC § 102

Claims 1-2 and 4-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Singh et al. (US 6,770,439).

Singh et al. teach a method for amplifying a signal from a binding assay comprising the steps of providing a reaction mixture comprising: a medium suspected of containing an analyte (see col. 9, lines 16-19, "a large number of proteins in a single sample"), a first specific binding pair member bound to a support (see col. 9, lines 21-22, "One group of binding proteins is bound to a support"), a second specific binding pair

member bound to a sensitizer (see col. 10, lines 22-28, "Two entities are employed... that bind to the same target moiety. One of the entities generates an active species") capable in its excited state of generating a reactive oxygen species (see col. 11, line 17, "Singlet oxygen"), wherein the proximity of the two specific binding pair members is modulated by the presence of analyte (see col. 39, lines 39-41, "The resulting complex has three components, where the target serves to link the labeled binding members to the support"), and a detectable substrate bound to the support through a reactive oxygen cleavable linker (see col. 10, lines 24-27, "a susceptible functionality that interacts with the active species resulting in release of the eTag reporter") (see col. 36, lines 32-35, "The solid support may have... e-tag probe covalently or non-covalently bound to the support"), incubating the reaction mixture (see col. 39, line 51, "mixture is incubated"), exciting the sensitizer causing the formation of reactive oxygen (see col. 11, line 17, "Singlet oxygen"), which cleaves the cleavable linker and releases detectable substrate from the support (see col. 10, lines 24-27, "One of the entities generates an active species. The other entity has a susceptible functionality that interacts with the active species resulting in release of the eTag reporter"), detecting the released detectable substrate (see Abstract, "Detection involves the release of identifying tags as a consequence of target recognition"), wherein the step of detecting comprises the steps of: separating the released detectable substrate from the detectable substrate associated with the support (see col. 36, lines 19-21, "the subject heterogeneous assays require that the unbound labeled reagent be separable from the bound labeled reagent"), adding to the separated released detectable substrate, a third specific binding pair member capable of binding directly to the released detectable substrate, allowing the third specific binding pair member to bind, and detecting the bound third specific binding pair member (see col. 29, lines 6-8, "biotin and strept/avidin... digoxin or derivative thereof and antidigoxin).

With respect to claim 2, Singh et al. teaches a method for amplifying a signal from a binding assay wherein the proximity of the first and second specific binding pair members results from the binding of the first and second specific binding pair members to the analyte (see col. 39, lines 35-41, "sandwich mode", "The resulting complex has three components, where the target serves to link the labeled binding members to the support"), the sensitizer is a photosensitizer (see col. 11, lines 6-7, "squarate

derivatives"), the reactive oxygen is singlet oxygen (see col. 11, lines 6-7, "singlet oxygen"), and the excitation step comprises irradiation with light (see col. 10, lines 18-19, "photoactivated excited species").

With respect to claims 4-6, Singh et al. teaches a method for amplifying a signal from a binding assay wherein the reactive oxygen cleavable linker comprises enamines (see col. 11, line 20), imidazole, oxazole, and thiazole (see col. 12, lines 29-30).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3 and 37-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (US 6,770,439) in view of Oh & Sternberg (US 5,851,778).

Singh et al. teach a method for amplifying a signal from a binding assay as described supra. In addition, Singh et al. teach a method wherein the analyte, first specific binding pair member, and second specific binding pair member are polynucleotides (see Figs. 3A, 3B), the substrate comprises digoxigenin-linked biotin (see col. 29, lines 6-8, "biotin and strept/avidin... digoxin or derivative thereof and antidigoxin), and detection employs avidin and anti-digoxigenin antibodies (see col. 29, lines 6-8, "biotin and strept/avidin... digoxin or derivative thereof and antidigoxin) bound to a member of a signal producing system.

Singh et al. do not teach a detectable substrate comprising digoxigenin-linked biotin.

However, Oh & Sternberg teach the use of digoxigenin-linked biotin (see col. 16, lines 30-38, "other tridentates", "digoxin") in energy transfer assays (see col. 17, lines 54+). Therefore, it would have been obvious for a person of ordinary skill in the art to modify the method for amplifying a signal from a binding assay with the use of digoxigenin-linked biotin because Oh & Sternberg discovered that tridentate conjugates do not require "expensive isolation and characterization procedures of prior art reagents" and exhibit "longer shelf life" than prior art counterparts (see col. 18, lines 51-63).

Claims 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (US 6,770,439) in view of Oh & Sternberg (US 5,851,778).

Singh et al. teach a method for amplifying a signal from a binding assay comprising the steps of providing a reaction mixture comprising: a medium suspected of containing an analyte (see col. 9, lines 16-19, "a large number of proteins in a single sample"), a first specific binding pair member bound to a support (see col. 9, lines 21-22, "One group of binding proteins is bound to a support"), a second specific binding pair member bound to a sensitizer (see col. 10, lines 22-28, "Two entities are employed... that bind to the same target moiety. One of the entities generates an active species") capable in its excited state of generating a reactive oxygen species (see col. 11, line 17, "Singlet oxygen"), wherein the proximity of the two specific binding pair members is modulated by the presence of analyte (see col. 39, lines 39-41, "The resulting complex has three components, where the target serves to link the labeled binding members to the support"), and a detectable substrate bound to the support through a reactive oxygen cleavable linker (see col. 10, lines 24-27, "a susceptible functionality that interacts with the active species resulting in release of the eTag reporter") (see col. 36, lines 32-35, "The solid support may have... e-tag probe covalently or non-covalently bound to the support"), incubating the reaction mixture (see col. 39, line 51, "mixture is incubated"), exciting the sensitizer causing the formation of reactive oxygen (see col. 11, line 17, "Singlet oxygen"), which cleaves the cleavable linker and releases detectable substrate from the

support (see col. 10, lines 24-27, "One of the entities generates an active species. The other entity has a susceptible functionality that interacts with the active species resulting in release of the eTag reporter"), detecting the released detectable substrate (see Abstract, "Detection involves the release of identifying tags as a consequence of target recognition").

Singh et al. do not teach a detectable substrate comprising digoxigenin-linked biotin.

However, Oh & Sternberg teach the use of digoxigenin-linked biotin (see col. 16, lines 30-38, "other tridentates", "digoxin") in energy transfer assays (see col. 17, lines 54+). Therefore, it would have been obvious for a person of ordinary skill in the art to modify the method for amplifying a signal from a binding assay with the use of digoxigenin-linked biotin because Oh & Sternberg discovered that tridentate conjugates do not require "expensive isolation and characterization procedures of prior art reagents" and exhibit "longer shelf life" than prior art counterparts (see col. 18, lines 51-63).

Response to Arguments

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of the term "substrate." Applicants argue that, according to the page 9, lines 5-22 of Applicants' Specification, the term "substrate" is clearly defined. Applicants' argument has been carefully considered but is not persuasive because, by Applicants' admission, the term "substrate" also equates to the term "product" (see Applicants' Remarks at page 13, lines 12-13, "The released substrate is also referred to in the Specification as the product."). Applicants' also submit argumentation explaining how the "substrate" is detected (see Applicants' Remarks at page 13, lines 17-22). However, it appear that Applicants' argumentation does not address the issue of whether the term "substrate" is indefinite, and will not be addressed here. Accordingly, this rejection is not withdrawn.

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of the term "cleavable linker." Applicants have amended claim 1 to further clarify the term "cleavable linker." Accordingly, this rejection is withdrawn.

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, for omitting essential steps relating a causal relationship between sensitizer excitation and release of substrate. Applicants have amended claim 1 to further clarify the causal relationship between sensitizer excitation and release of substrate. Accordingly, this rejection is withdrawn.

In prior Office Action, claims 5-6 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of "dioxenes, thioxenes, oxazines" and for not adequately explaining how cleavage of the recited linkers results in release of detectable substrate. Applicants argue that the paragraph bridging pages 37-38 provides adequate explanation for claims 5-6. Examiner notes that the cited paragraph appears to describe the use of dioxenes, thioxenes, oxazines, dithienes, oxazoles, anthracenes, and diacylhydrazides as cleavable linkers. Accordingly, this rejection is withdrawn.

In prior Office Action, claim 9 (now incorporated into claim 1) was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of "or indirectly." Applicants argue that the phrase "capable of binding directly or indirectly" is adequately defined on page 54, lines 6-10 of the Specification. Applicants' argument has been carefully considered but is not persuasive because the phrase "capable of binding directly or indirectly" is not adequately defined on page 54, lines 6-10 of the Specification. According to page 54, lines 6-10 of the Specification, the phrase "capable of binding... indirectly" means that an entity can "bind specifically to a specific binding pair member or to a complex of two or more sbp members which is capable of binding the other analyte or assay component (indirectly)." However, the cited portion of page 54, lines 6-10 of the Specification further confounds the term "indirectly" because it is not clear how the limitations of claim 9 are analogous to "a specific binding pair member" or "a complex

of two or more sbp members" or "other analyte" or "assay component". Accordingly, this rejection is not withdrawn.

In prior Office Action, claims 1-6 and 9 were rejected under 35 U.S.C. 102(e) as being anticipated by Singh et al. (US 6,770,439). Applicants have amended claim 1 to add, inter alia, "a third specific binding pair member capable of binding directly or indirectly to the released detectable substrate." Applicants argue that Singh et al. do not teach "a third specific binding pair member capable of binding directly or indirectly to the released detectable substrate." In addition, Applicants argue that the "capture ligand" or "capture agent" of Singh et al. does not amount to a teaching of "a third specific binding pair member capable of binding directly or indirectly to the released detectable substrate" because Singh et al. teach a "capture ligand" or "capture agent" that is limited in use for "separating uncleaved e-tag probes from released e-tag reporters" (see Applicants' Remarks at page 16, lines 3-4). Applicants' argument has been carefully considered but is not persuasive because it appears that the "capture ligand" or "capture agent" of Singh et al. is not so limited in use for "separating uncleaved e-tag probes from released e-tag reporters." For example, Singh et al. teach that e-tags can be reacted with a detectable label before or after the e-tag reporters are released or cleaved (see col. 40, lines 25-41). Accordingly, this rejection is not withdrawn.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J Venci
Examiner
Art Unit 1641

djv

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03/16/05